

10/532153

Rec'd PTO 20 APR 2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number  
**WO 2004/042365 A3**

(51) International Patent Classification<sup>7</sup>: C12Q 1/68, (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:  
PCT/US2003/036247

(22) International Filing Date:  
3 November 2003 (03.11.2003)

(25) Filing Language: English

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(30) Priority Data:  
60/423,113 1 November 2002 (01.11.2002) US

(71) Applicant (*for all designated States except US*): EVOLUTIONARY GENOMICS LLC [US/US]; Bioscience Park Center, 12635 East Montview Boulevard, Suite 211, Aurora, CO 80010 (US).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): MESSIER, Walter [US/US]; 2418 Bowen Street, Longmont, CO 80501 (US).

(88) Date of publication of the international search report:  
24 February 2005

(74) Agents: SWANSON, Barry, J. et al.; Swanson & Bratschun, L.L.C., 1745 Shea Center Drive, Suite 330, Highlands Ranch, CO 80129 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/042365 A3

(54) Title: DEVELOPMENT OF THERAPEUTICS FOR THE TREATMENT OF ENDOTOXIN-MEDIATED DISEASES

(57) **Abstract:** The subject invention comprises a method for identifying an evolutionarily meaningful nucleotide change in a primate's *TLR4* polynucleotide. It further comprises methods for identifying agents that interact with the corresponding evolutionarily meaningful amino acid change so as to modulate the function of the *TLR4* polypeptide, thereby attenuating activation of the NF- $\kappa$ B pathway. Such agents are useful in mitigating the LPS mediated response and in the treatment of sepsis, severe sepsis and septic shock.